

## INTERVENTIONAL CARDIOLOGY AND SURGERY

## Prognostic implication of cardiac troponin T increase following stent implantation

J Herrmann, C von Birgelen, M Haude, L Volbracht, N Malyar, H Eggebrecht, T F M Konorza, D Baumgart, R Erbel

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**Objective:** To identify the incidence and clinical significance of myocardial injury following elective stent implantation.

**Design:** Prospective clinical study with 278 consecutive patients undergoing stenting of de novo coronary or saphenous vein graft lesions. Incidence of periprocedural myocardial injury was assessed by analysis of 12 lead ECG, creatine kinase (CK; upper limit of normal (ULN) 70 IU/l for women, 80 IU/l for men), and cardiac troponin T (cTnT; point of care test; threshold 0.1 ng/ml) before and 6, 12, and 24 hours after the intervention. Major adverse cardiac events (MACE: acute myocardial infarction, bypass surgery, and cardiac death) were recorded during clinical follow up (mean (SD) 7.8 (5.3) months).

**Results:** Following elective stenting, the rate of a positive cTnT status was 17.3%, the rate of CK increase of 1–3× ULN 14.7%, the rate of CK increase of > 3× ULN 1.4%, and the rate of Q wave myocardial infarction 0.4%. Cardiac mortality during follow up was higher in patients with postprocedurally increased CK (7.1% v 1.3%,  $p = 0.01$ , log rank) and cTnT (9.1% v 0.9%,  $p < 0.001$ , log rank). In addition, postprocedurally increased cTnT was associated with a higher overall incidence of MACE (13.1% v 4.0%,  $p < 0.01$ , log rank) and was identified as an independent factor for MACE during follow up (hazard ratio 3.27, 95% confidence interval 1.14 to 9.41,  $p = 0.028$ ).

**Conclusions:** Following elective stent implantation, a positive cTnT status identified patients at risk of a worse long term outcome. Treatment strategies have to be developed that lead to prognostic improvement by reducing periprocedural myocardial injury.

See end of article for authors' affiliations

Correspondence to: Professor R Erbel, University of Essen, Division of Internal Medicine Department of Cardiology, Hufelandstrasse 55, D-45122 Essen, Germany; erbel@uni-essen.de

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During the past two decades, coronary stenting either with predilatation (conventional stenting) or without predilatation (direct stenting) has become the leading type of percutaneous coronary intervention, and accounts for approximately 70% of all catheter based procedures.<sup>1–4</sup> Increasing experience, use of novel stent designs, and more effective antiplatelet treatment contributed to this development.<sup>5–6</sup> Yet the favourable impact on both short and long term clinical outcome remained the most important factor in the widespread use of stent implantation.<sup>1–3</sup>

Fundamental questions in clinical practice were, however, raised by various clinical trials, which showed a worse long term outcome for patients with increased creatine kinase (CK) following otherwise successful percutaneous coronary intervention.<sup>7</sup> By means of postprocedural analysis of cardiac troponin T (cTnT) or cardiac troponin I, even minor forms of these intervention related events have become detectable and were found to be higher with stent implantation than with balloon angioplasty.<sup>8–9</sup> Yet the prognostic significance of these minor forms of stenting related myocardial injury is still unknown.

Thus, the present study was designed to assess prospectively the incidence and prognostic significance of myocardial injury associated with direct and conventional stent implantation by serial analysis of cTnT, CK, and 12 lead ECG.

## METHODS

## Patient population

Between January 1998 and November 1999, all patients with successful single vessel stenting were included in this study unless they met at least one the following criteria: increased cardiac serum markers before intervention; acute myocardial

infarction (AMI) during the two weeks before the procedure; terminal renal insufficiency, hypothyroidism, or skeletal muscle injury; vessel diameter < 2.5 mm; severe calcification or angulation of the target lesion; in-stent restenosis or chronic occlusion; and contraindication for aspirin, ticlopidine, or clopidogrel medication.

Procedural success was defined as a reduction in stenosis diameter < 30% without fatal complications or emergency coronary artery bypass grafting. The study was approved by the local council of human research and all patients gave written informed consent for the coronary procedure.

## Interventional procedure

All interventional procedures were performed through the femoral route using tubular slotted stents only. It was left to the operator's discretion to choose between conventional stenting and direct stenting based on the vessel anatomy and personal preference. If angiography suggested incomplete stent expansion or residual stenosis > 30%, further high pressure balloon inflations were performed. After the procedure, ticlopidine (500 mg/day) or clopidogrel (300 mg initial bolus, followed by 75 mg/day) was given for four weeks in addition to lifelong aspirin medication (100 mg/day).

Angiographic lesion characteristics were classified according to the modified American Heart Association/American

**Abbreviations:** AHA/ACC, American Heart Association/American College of Cardiology; AMI, acute myocardial infarction; CK, creatine kinase; cTnT, cardiac troponin T; EPISTENT, evaluation of platelet IIb/IIIa inhibitor for stenting; MACE, major adverse cardiac events; OR, odds ratio; SVG, saphenous vein graft; ULN, upper limit of normal

**Table 1** Demographic profile of the study population

	Overall (n=278)	cTnT negative (n=230)	cTnT positive (n=48)
Age (years)	61.5 (8.9)	61.4 (9.2)	62.3 (7.9)
Age >75 years	13 (4.7)	12 (5.2)	1 (2.1)
Male sex	221 (79.5)	185 (80.4)	36 (75.0)
Unstable AP	27 (9.7)	22 (9.6)	5 (10.4)
Multivessel CAD	209 (75.2)	169 (73.5)	40 (83.3)
Prior AMI	114 (41.0)	88 (38.3)	26 (54.2)
Prior CABG	82 (29.5)	66 (28.7)	16 (33.3)
Prior PCI	129 (46.4)	107 (46.5)	22 (45.8)
LVEF <30%	6 (2.2)	2 (0.9)	4 (8.3)*
Family history	49 (17.6)	39 (17.0)	10 (20.8)
Obesity	47 (16.9)	35 (15.2)	12 (25.0)
Hypercholesterolaemia	228 (82.0)	192 (83.5)	36 (75.0)
Systemic hypertension	166 (59.7)	138 (60.0)	28 (58.3)
Diabetes mellitus	54 (19.4)	44 (19.1)	10 (20.8)
Cigarette smoking	78 (28.1)	64 (27.8)	14 (29.2)

Data are n (%) or mean (SD) (age).

\*p<0.001 versus cardiac troponin T (cTnT) negative.

AP, angina pectoris; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

College of Cardiology (AHA/ACC) classification.<sup>10</sup> All procedural complications were noted and were based on commonly used definitions.<sup>11</sup> Missing or severely impaired flow in the presence of an apparently open coronary vessel was defined as “no reflow”.

### Cardiac marker analysis

Venous blood sampling and 12 lead ECG were scheduled before as well as 6, 12, and 24 hours after the coronary intervention. Total CK serum activity was determined by an enzymatic assay (Bayer Diagnostics, Leverkusen, Germany; activator: N-acetylcysteine, Merck, Darmstadt, Germany) with an upper limit of normal (ULN) of 70 IU/l for women and 80 IU/l for men. cTnT was analysed using a rapid bedside test (Cardiac T, Roche Diagnostics, Mannheim, Germany) with a threshold of 0.1 ng/ml.<sup>12</sup> New Q waves were defined as those at least 30 ms wide and deeper than 25% of the correlating R amplitude in at least two of the three diaphragmatic leads (II, III, aVF), in at least two of the four anteroseptal leads (V1 to V4), or in at least two of the lateral leads (V5, V6, I, aVL).<sup>13</sup>

### Clinical follow up

Follow up data were obtained by telephone interviews with the patient, their relatives, their primary physician, or their cardiologist at six month intervals. A standardised format was used to record hospitalisation for unstable angina pectoris, target lesion revascularisation, target vessel revascularisation, and major adverse cardiac events (MACE: coronary artery bypass grafting, AMI, and cardiac death). AMI during follow up was defined biochemically by a minimum rise of CK > 2× ULN or electrocardiographically by the development of new Q waves. Deaths were classified as being of cardiac origin if they were associated with congestive heart failure, arrhythmia, AMI, sudden death (> 1 hour after onset of cardiac symptoms), or any other cardiac malady.

### Statistical analysis

Data were analysed using the SPSS software package (version 10.1, SPSS, Chicago, Illinois, USA). Continuous variables are reported as mean (SD) and categorical variables as percentages. Group comparisons were made by Student's *t* test or U

**Table 2** Interventional profile of the study population

	Overall (n=278)	cTnT negative (n=230)	cTnT positive (n=48)
Direct stenting	105 (37.8)	88 (38.3)	17 (35.4)
Target vessel			
LAD	88 (31.7)	74 (32.2)	14 (29.2)
LCX	58 (20.9)	45 (19.6)	13 (27.1)
RCA	81 (29.1)	71 (30.9)	10 (20.8)
RIM	8 (2.9)	8 (3.5)	0 (0.0)
SVG	43 (15.5)	32 (13.9)	11 (22.9)
Lesion characteristics			
AHA/ACC type A	21 (7.6)	17 (7.4)	4 (8.3)
AHA/ACC type B1	138 (49.6)	123 (53.5)	15 (31.3)*
AHA/ACC type B2	92 (33.0)	75 (32.6)	17 (35.4)
AHA/ACC type C	27 (9.7)	15 (6.5)	12 (25.0)**
Complications			
Dissection	9 (3.2)	4 (1.7)	5 (10.4)*
Side branch occlusion	14 (5.0)	12 (5.2)	2 (4.2)
Vasospasm	3 (1.1)	2 (0.9)	1 (2.1)
No reflow	2 (0.7)	0 (0.0)	2 (4.2)*
Medication			
Abciximab	16 (5.8)	12 (5.2)	4 (8.3)
Ticlopidine	224 (80.6)	189 (82.2)	35 (72.9)
Clopidogrel	54 (19.4)	41 (17.8)	13 (27.1)

Data are n (%). \*p<0.01; \*\*p<0.001 versus cTnT negative.

AHA/ACC, American Heart Association/American College of Cardiology; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; RIM, intermediate branch; SVG, saphenous vein graft.

**Table 3** Postprocedural cardiac marker outcome

	Overall (n=278)	cTnT negative (n=230)	cTnT positive (n=48)
Peak CK (IU/l)	56 (55)	46 (30)	105 (102)*
CK 1–3× ULN	41 (14.8)	20 (8.7)	21 (43.8)*
CK >3× ULN	4 (1.4)	0 (0.0)	4 (8.3)*
Q wave MI	1 (0.4)	0 (0.0)	1 (2.1)

Data are n (%) or mean (SD) (peak creatine kinase [(CK)]. \*p<0.001 versus cTnT negative.

MI, myocardial infarction; ULN, upper limit of normal.

**Table 4** Long term clinical outcome

	Overall (n=269)	cTnT negative (n=225)	cTnT positive (n=44)
Follow up (months)	7.8 (5.3)	8.1 (5.4)	7.1 (4.3)
TVR	62 (23.1)	51 (22.7)	11 (25.0)
TLR	44 (16.4)	37 (16.4)	7 (15.9)
Unstable AP	18 (6.7)	15 (6.7)	3 (6.8)
AMI	2 (0.7)	1 (0.4)	1 (2.3)
CABG	7 (2.6)	6 (2.7)	1 (2.3)
Death	6 (2.2)	2 (0.9)	4 (9.1)*
MACE	15 (5.6)	9 (4.0)	6 (13.6)**

Data are n (%) or mean (SD) (follow up period). \*p=0.001;

\*\*p=0.01 versus cTnT negative.

MACE, major adverse cardiac events (AMI, CABG, death); TLR, target lesion revascularisation; TVR, target vessel revascularisation.

test (continuous parametric or non-parametric data, respectively) or by  $\chi^2$  test in case of categorical variables. Odds ratio (OR) and 95% confidence intervals (95% CI) are given for variables correlating significantly with postprocedural cardiac marker increase and MACE during follow up in univariate and multivariate logistic regression analyses. Cumulative (event free) survival was analysed by the Kaplan-Meier method and group comparison was done by the log rank test. The multivariate Cox proportional hazards regression model was used to analyse the independent association of variables with MACE during follow up (hazard ratio, 95% CI). A probability value of  $p < 0.05$  was considered significant.

## RESULTS

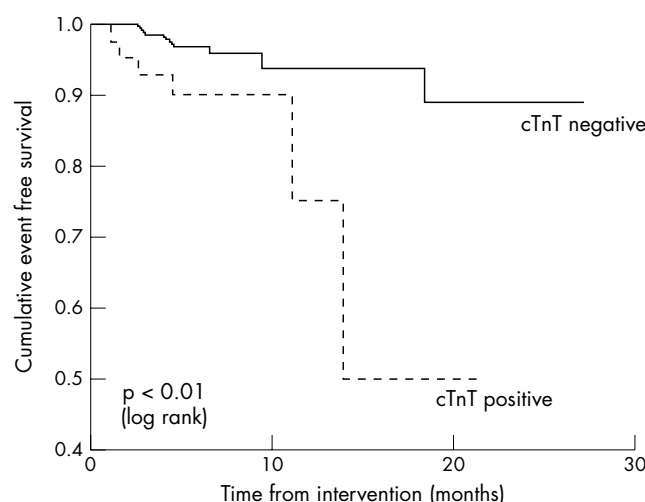
### Patient population

Table 1 and table 2 present the demographic and interventional profiles for the entire study population ( $n = 278$ ) stratified according to cTnT outcome. There was no significant difference between the postprocedurally cTnT positive and postprocedurally cTnT negative patients in procedural parameters such as number of stents, maximal inflation pressure, balloon to artery ratio, and stenosis grade before and after intervention (data not shown).

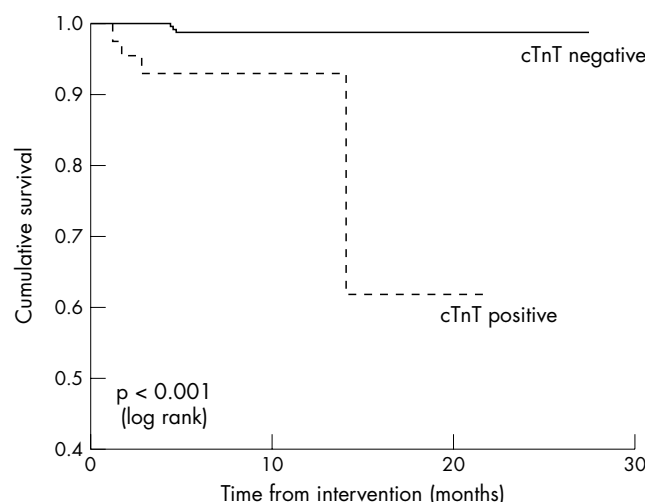
### Cardiac marker outcome

Overall, the rate of postprocedural increase of cTnT was 17.3%, the rate of CK increase of 1–3× ULN 14.7%, the rate of CK increase of > 3× ULN 1.4%, and the rate of Q wave myocardial infarction 0.4%. Table 3 shows the association between postprocedural cTnT increase and CK outcome.

Variables that correlated with a postprocedural cTnT increase in the univariate logistic regression analysis were a < 30% reduction in left ventricular ejection fraction before intervention (OR 12.14, 95% CI 2.13 to 69.31,  $p = 0.005$ ), ACC/AHA type B1 lesions (OR 0.4, 95% CI 0.2 to 0.77,  $p = 0.006$ ), ACC/AHA type C lesions (OR 4.78, 95% CI 2.07 to 11.04,  $p < 0.001$ ), and dissection (OR 6.57, 95% CI 1.7 to 25.5,  $p = 0.006$ ). Postprocedural CK was associated with a family history of coronary artery disease (OR 0.19, 95% CI 0.04 to 0.79,  $p = 0.023$ ), saphenous vein graft (SVG) intervention (OR



**Figure 1** Event-free survival for patients with postprocedurally increased cardiac troponin T (cTnT pos;  $n = 44$ ) and patients without postprocedurally increased cTnT (cTnT neg;  $n = 225$ ).



**Figure 2** Kaplan-Meier survival curves for patients with postprocedurally increased cTnT (cTnT pos;  $n = 44$ ) and patients without postprocedurally increased cTnT (cTnT neg;  $n = 225$ ).

2.37, 95% CI 1.11 to 5.07,  $p = 0.026$ ), and ACC/AHA type C lesions (OR 3.63, 95% CI 1.54 to 8.57,  $p = 0.031$ ).

Multivariate logistic regression analysis identified ACC/AHA type C lesions (OR 5.01, 95% CI 1.58 to 15.87,  $p = 0.006$ ) and a < 30% reduction in left ventricular ejection fraction before intervention (OR 14.23, 95% CI 2.31 to 87.67,  $p = 0.004$ ) as independent predictors of a postprocedural increase in cTnT. Family history (OR 0.19, 95% CI 0.45 to 0.84,  $p = 0.028$ ) and ACC/AHA type C lesions (OR 2.95, 95% CI 1.09 to 7.97,  $p = 0.033$ ) were independently associated with CK increase.

### Clinical follow up

Follow up data were available for 96.8% of the patients (table 4). The overall incidence of MACE during follow up was higher in patients with a positive postprocedural cTnT status (OR 3.79, 95% CI 1.28 to 11.26,  $p = 0.016$ ) (fig 1). SVG intervention was the only other variable that correlated with MACE in the univariate logistic regression analysis (OR 4.17, 95% CI 1.40 to 12.44,  $p = 0.01$ ). Multivariate logistic regression and Cox proportional hazards analyses identified a positive postprocedural cTnT status (OR 3.53, 95% CI 1.16 to 10.74,  $p = 0.026$  and hazard ratio 3.27, 95% CI 1.14 to 9.41,  $p = 0.028$ , respectively) and SVG intervention (OR 3.9, 95% CI 1.28 to 11.88,  $p = 0.017$

and hazard ratio 2.95, 95% CI 1.02 to 8.54,  $p = 0.046$ ) as independently associated with MACE during follow up.

Differences in MACE were caused mainly by differences in cardiac mortality, which was higher in patients with a positive postprocedural cTnT status (OR 11.14, 95% CI 1.98 to 62.87,  $p = 0.006$ , fig 2) and in patients with a postprocedural CK increase (OR 5.74, 95% CI 1.12 to 29.49,  $p = 0.036$ ). Other variables that correlated with survival in the univariate logistic regression analysis were a  $< 30\%$  reduction in left ventricular ejection fraction (OR 16.42, 95% CI 1.39 to 194.121,  $p = 0.03$ ), SVG intervention (OR 12.21, 95% CI 2.16 to 69.03,  $p = 0.005$ ), and a postprocedural CK increase of  $> 3 \times$  ULN (OR 26.1, 95% CI 2.02 to 337.07,  $p = 0.012$ ). SVG intervention was the only variable that was independently associated with cardiac mortality during follow up (OR 18.48, 95% CI 1.71 to 199.47,  $p = 0.016$ ; hazard ratio 10.48, 95% CI 1.05 to 104.2,  $p = 0.045$ ).

## DISCUSSION

The present study shows that a positive cTnT status following elective stent implantation is associated with a worse long term clinical outcome despite a low in-hospital rate of MACE.

### Periprocedural myocardial injury

Ever since the issue of periprocedural myocardial injury arose in the 1990s, there has been considerable debate about the clinical significance of these intervention related events.<sup>14</sup> Although reversible myocardial ischaemia can lead to release of cardiac enzymes,<sup>15</sup> it is generally accepted that an increase in cardiac serum markers reflects myocardial necrosis in the majority of cases. Notably, cardiac troponins are considered to be highly specific and sensitive markers of irreversible myocardial injury.<sup>16</sup> Following elective stent implantation, a cTnT increase of  $> 0.1$  ng/ml and increased CK/CK-MB  $> 1 \times$  and  $> 3 \times$  ULN have been reported in 3–29%, 3–35%, and 0–10% of patients, respectively.<sup>8, 17–22</sup>

In the present study, a postprocedural increase of cTnT and of CK  $> 1 \times$  ULN were noted in similar frequency, yet in only half of the cases concomitantly. Considering that the overall incidence of a CK increase  $> 3 \times$  ULN was low and always associated with a cTnT increase, the discrepancy in cardiac marker outcome was limited mainly to cases in which the CK increase was mild. Thus, following successful stent implantation, minor rather than major myocardial injury can be found frequently, with cTnT being of higher diagnostic value than CK. In line with previous trials, patients with a baseline reduction of left ventricular function and more complex target lesions are at higher risk of these events.<sup>7, 18, 23</sup>

### Prognostic significance

In a series of angioplasty trials evaluating the clinical implication of peri-interventional myocardial injury, some, though not all, studies showed the prognostic significance of postprocedural CK or CK-MB increase.<sup>7, 8, 24–27</sup> In the EPISTENT trial (evaluation of platelet IIb/IIIa inhibitor for stenting), an increase of CK/CK-MB  $> 3 \times$  ULN following stent implantation was associated with higher mortality during follow up.<sup>28</sup> Saucedo and colleagues<sup>21</sup> confirmed the association between postprocedurally increased cardiac enzyme and future MACE (mainly cardiac mortality), albeit with a “prognostic” threshold concentration of  $5 \times$  ULN. On the contrary, Gabarz and colleagues<sup>19</sup> found neither CK nor cardiac troponin I increase to be predictive of future adverse events in a series of 109 consecutive patients undergoing stent implantation.

Although the study size has to be taken into consideration, the correlation of cardiac mortality and overall MACE was found to be stronger with postprocedurally increased cTnT than with postprocedurally increased CK. As a concomitant increase of CK  $> 3 \times$  ULN was present in only a few cases of postprocedural cTnT increase, the clinical significance of

minor rather than major peri-interventional myocardial injury is furthermore highlighted by these findings. Thus, following elective stent implantation, the present study identifies cTnT as a better prognostic marker than CK and underscores the prognostic implication of even minor intervention related myocardial injury.

### Clinical implication

As shown in this and other studies, a postprocedural cardiac marker increase is neither a rare nor a prognostically insignificant event. Given the current findings, postprocedural cTnT increase in particular seems to be of diagnostic and clinical value. The diagnostic window of cTnT and the use of point of care testing in this study furthermore suggest that, following stent implantation, patients at risk of future MACE and increased cardiac mortality can be identified by any increase of cTnT within a day after the procedure. Thus, cTnT analysis proves to be useful for further risk stratification after stent implantation.

As far as prevention of any of these events is concerned, filter or balloon occlusion systems have increasingly become of interest.<sup>29, 30</sup> Their potential to prevent embolisation of debris and peri-interventional myocardial injury has been shown in interventions for SVG lesions.<sup>29</sup> The efficacy of their use in intervention of native coronary arteries, as well as their use in general, remains to be proved on a larger scale. In one larger monocentre study, peri-interventional  $\beta$  blocker treatment was found to reduce the risk of peri-interventional myocardial injury.<sup>18</sup> On a broader, multicentre scale, glycoprotein IIb/IIIa receptor inhibitors have been shown to prevent at least major forms of peri-interventional myocardial injury.<sup>20, 22</sup> Their impact on minor forms of myocardial injury related to stent implantation, however, has not been studied.

### Limitations and potential sources of error

As the size of the present study is small, results must be interpreted with caution. Given a study size of 269 patients with follow up data and cardiac mortalities of 9.1%  $v$  0.9% (MACE of 13.6%  $v$  4.0%) in patients with versus those without postprocedural cTnT increase, the power of the present study can be retrospectively calculated to be 0.782 (0.659). Furthermore, semiquantitative cTnT analysis was used in this study, excluding the possibility of stratification of patient outcome according to increments of marker increase. Moreover, the chance of very small rises and peak serum concentrations between the intervals of blood analysis cannot be excluded. However, the entire study population would have been affected to the same extent by this putative systematic error.

### Conclusion

Following stent implantation, an increase in cTnT can identify patients at risk of a worse long term clinical outcome despite low in-hospital morbidity and mortality. New treatment strategies have to be developed to prevent periprocedural myocardial injury, which, even in minor forms, is associated with a worse long term outcome. Especially in situations of increased risk such as intervention for complex lesion types, use of glycoprotein IIb/IIIa receptor inhibitors and distal protection devices may prove beneficial for further improvement of acute and long term outcome following stent implantation.

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### Authors' affiliations

J Herrmann, C von Birgelen, M Haude, N Malyar, H Eggebrecht, T F M Konorza, D Baumgart, R Erbel, Department of Cardiology, University Hospital Essen, Essen, Germany  
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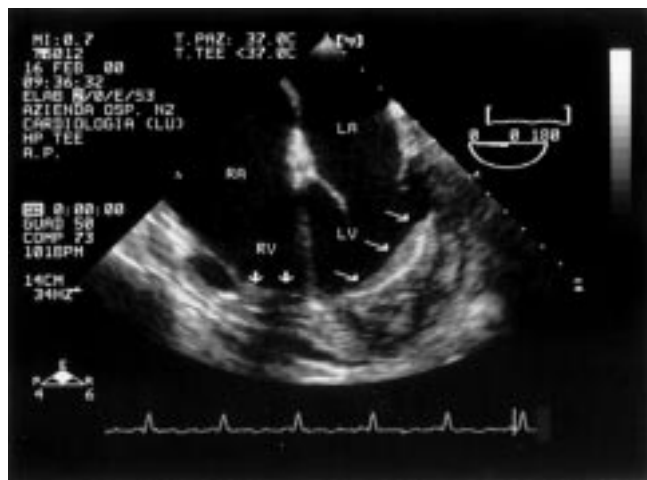


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## IMAGES IN CARDIOLOGY

### Cardiac involvement in idiopathic hypereosinophilic syndrome

A 38 year old man was referred for dyspnoea. Transthoracic and transoesophageal echocardiography revealed the presence of deposits at the apex of the left and right ventricle (arrows). Routine blood tests showed an increased eosinophil count ( $18 \times 10^9$ /litre). A bone marrow biopsy demonstrated an eosinophilic myeloproliferative disease. The patient was diagnosed with hypereosinophilic syndrome, in which cardiac involvement is common.



liferative disease. The patient was diagnosed with hypereosinophilic syndrome, in which cardiac involvement is common.

The patient was treated with alpha interferon plus oral methylprednisolone. Concomitant treatment with diuretics and oral anticoagulants was also instituted. His symptoms improved and no further increase of the endomyocardial deposits was observed.

There are three stages in hypereosinophilic syndrome: necrotic, thrombotic, and fibrotic. Common echocardiographic findings in this disease are mural thrombus with apical cavity obliteration (which was the main manifestation in our patient) and thickening of the myocardium. Atrioventricular valves are often involved in the fibrotic process with subsequent valvar regurgitation. A restrictive pattern is typical of the late stage of the disease.

However, in our patient no sign of a restrictive pattern was evident. In fact, Doppler (pulmonary veins and transmitral flow) and nuclear (peak filling rate and time to peak filling rate) indexes of left ventricular compliance were normal.

According to the normal appearance of the spared myocardium and the atrioventricular valves, the fibrotic stage has yet to occur in this patient. Early institution of, and favourable response to, treatment may halt the fibrotic process and improve symptoms and prognosis in these patients.

**R Lorenzoni**  
**L Cortigiani**  
**A Melosi**

lorenzoni.r@tin.it